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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,494	08/16/2001	Reid W. Von Borstel	1331-352	1560

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/21/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,494	VON BORSTEL ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *16,17,42-46 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18-41 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-11, 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 16 dated July 21, 2003 is acknowledged.

2. Claims 16-17, 42-46, and 50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 16 dated July 21, 2003. Election is MADE FINAL.

Double Patenting

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 22, 24, 26, 28-30 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 48-53 and 62 of copending Application No. 09/763,955. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-15, 21, 23, 27, 31-32, 37-41, and 47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-59 of copending Application No. 09/763,955. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-15 differ from the invention of the '955 application in that the '955 does not limit the source or cause of the respiratory chain dysfunction; however, the source of the respiratory chain dysfunction is not seen to result in a patentably distinguishable methodological difference. In other words, the source or cause of the respiratory chain dysfunction is not seen to be of patentable import as such relates to the procedural steps of the method claimed.

Claims 21, 23, 27, and 31-32 the invention of the '955 application differ in scope with regards to the conditions being treated or prevented; however, the claims of the '955 application and the instant invention overlap substantially, and to issue a patent to

the claims of the instant application could extend the patent term for subject matter the '955 application.

Claims 37-41 differ from the invention of the '955 application in that the invention of the '955 application is not limited to treatment (reads on prevention); however, the methodological steps and active agents employed by both methods are the same.

Claim 47 differs from the invention of the '955 application in that the invention of the '955 application does not limit the pyrimidine nucleotide precursor to pyruvic acid or ester thereof; however, the '955 application teaches that uridine tripyruvate provides the benefits of both pyrimidines and pyruvate for the treatment of cells with defective mitochondrial function (pages 14).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

7. Claims 22 and 38 are objected to because of the following informalities: the abbreviations should refer readers to the terms from which said abbreviation arises. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-15, 18-32, and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, does not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claims 1-15, 18-32, and 47-49 are drawn to a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering an effective amount of a pyrimidine nucleotide. Claims 2-15 limit cause of the respiratory chain dysfunction. Claims 18-21 limit the mode of administration of the active agent. Claims 22-32 limit the conditions treated or prevented. Claims 47-49 further require the administration of pyruvic acid, a pharmaceutically acceptable salt thereof, or a pyruvic acid ester.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to compounds and methods for treatment and prevention of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. Pyrimidine nucleotide precursors are administered to a mammal, including a human, for the purpose of compensating for mitochondrial dysfunction and for improving mitochondrial functions.

The treatment of diseases involving mitochondrial dysfunction is well known in the art. Treatment generally involves the administration of vitamins and cofactors used by particular elements of the mitochondrial respiratory chain.

A person of ordinary skill in the art would be a M.D. or a medicinal chemist having a PhD degree or higher.

In the instant case, examples drawn to treatment is not seen as sufficient to support the alleged applicability for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and

pathophysiological consequences of mitochondrial respiratory chain dysfunction. Insufficient data has been presented which demonstrates that congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, or pathophysiological consequences of mitochondrial respiratory chain dysfunction is prevented by the administration of a pyrimidine nucleotide precursor as instantly claimed.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use if for themselves, see *In re Gardner et al*, 166 USPQ 138 (CCPA 1970). Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the prevention of congenital mitochondrial disease, Alzheimer's disease, Huntington's disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction.

10. Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 33-36 are drawn to a method for preventing death or functional decline of post-mitotic cells in a mammal due to mitochondrial respirator chain dysfunction comprising administration of an effective amount of a pyrimidine nucleotide precursor. Claims 34-36 limit the nature of said post-mitotic cells.

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to compounds and methods for treatment and prevention of diseases, developmental delays, and symptoms related to mitochondrial dysfunction. Pyrimidine nucleotide precursors are administered to a mammal, including a human, for the purpose of compensating for mitochondrial dysfunction and for improving mitochondrial functions.

The treatment of diseases involving mitochondrial dysfunction is well known in the art. Treatment generally involves the administration of vitamins and cofactors used by particular elements of the mitochondrial respiratory chain.

A person of ordinary skill in the art would be a M.D. or a medicinal chemist having a PhD degree or higher.

In the instant case, examples drawn to treatment is not seen as sufficient to support the alleged applicability for the prevention of death or functional decline of post-mitotic cells. Insufficient data has been presented which demonstrates that death or functional decline of post-mitotic cells is prevented by the administration of a pyrimidine nucleotide precursor as instantly claimed.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use if for themselves, see *In re Gardner et al*, 166 USPQ 138 (CCPA 1970). Indeed, in view of the information set forth supra, the instant disclosure is not seen to be

sufficient to enable the prevention of death or functional decline pf post-mitotic cells in a mammal.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-15, 18, 21-41, and 47-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "an effective amount" renders all claims in which it appears indefinite as the function which is to be achieved is not stated in the claims and more than one effect can be implied from the specification or relative art.

The phrase "a pyrimidine nucleotide precursor" renders all claims in which the phrase appears indefinite. In the absence of distinct chemical core, distinct language to describe the structural modifications, or the chemical names of precursor compounds of this invention, the identity of said precursors would be difficult to describe and the metes and bounds of said precursor compounds applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1-15, 18-32, and 37-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Page et al. Proc. Natl. Acad. Sci. USA, 1997, Vol. 94, pages 11601-11606 (Page) in combination with von Borstel et al. U.S. Patent 6,316,426 B1 (von Borstel).

Claims 1-15 and 18-32 are drawn to a method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering an effective amount of a pyrimidine nucleotide. Claims 2-15 limit cause of the respiratory chain dysfunction. Claims 18-21 limit the mode of administration of the active agent. Claims 22-32 limit the conditions treated or prevented. Claims 37-41 are drawn to a method for treating developmental delay in cognitive, motor, language, executive function, or social skills in a mammal comprising administration of an effective amount of a pyrimidine nucleoside.

Page teaches the treatment of patients described with a syndrome that included developmental delay, seizures, ataxia, recurrent infections, severe language deficit, and an unusual behavioral phenotype characterized by hyperactivity, short attention span,

and poor social interaction with uridine (Abstract). Patients were treated with 50-1,000 mg/kg per day uridine (page 11604, column 2).

Page differs from the instantly claimed invention in that Page does not teach the use of acyl derivatives of uridine nor does Page explicitly teach all the conditions within the scope of the instantly claimed invention. However, these deficiencies would have been obvious to one of ordinary skill in the art at the time of the invention when viewed in combination with von Borstel.

von Borstel teaches a family of uridine and cytidine derivatives for the treatment of a variety of disorders including heart, muscle, plasma, liver, bone, diabetic, and neurological conditions (column 8, lines 20-24). The acyl derivatives of uridine comprise compounds having the formula (II) wherein R is an acyl radical of an unbranched fatty acid, an amino acid, a dicarboxylic acid, or a carboxylic acid selected from one or more of the group consisting of glycolic acid, pyruvic acid, orotic acid, and creatine (column 9. lines 1-23). 2',3'5'-tri-O-acetyl uridine is taught as being a preferred active agent (column 10, lines 2-5). The invention contemplates the use of these acyl derivatives for treating a variety of physiological and pathological conditions, including treatment of cardiac insufficiency and myocardial infarction, treatment of liver disease or damage, muscle performance, treatment of lung disorders, diabetes, central nervous system disorders such as cerebrovascular disorders, Parkinson's disease, and senile demetias (column 10, lines 24-35).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat patients having a mitochondrial disease with an acylated derivative of

uridine as taught by the prior art. The examiner recognizes that all of the conditions listed as being treatable/preventable by the instant uridine compounds are not explicitly embraced by the prior art; however, applicant has merely found a new property of the instant uridine compounds and such a discovery does not constitute a new use. In the instant case, the population to be treated is a subject having a mitochondrial disease. The prior art teaches the treatment of this population with an acylated derivative of uridine rendering the instantly claimed method *prima facie* obvious.

Conclusion

16. Claims 1-50 are pending. Claims 16-17, 42-46, and 50 are withdrawn from consideration as being drawn to a nonelected invention. Claims 1-15, 18-41, and 47-49 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 10:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
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